From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
GARY J. CONNELL
SHERIDAN ROSS P.C.
1560 BROADWAY
SUITE 1200
DENVER, CO 80202-5141

PCT

WRITTEN OPINION

(PCT Rule 66)

Applicant's or agent's file reference	Date of Mailing (*day/month/year*) 15 JUN 2001
4152-3-PCT	REPLY DUE within 2 months/days from the above date of mailing
International application No. PCT/US00/19336	International filing date (*day/month/year*) 13 July 2000 (13.07.2000)
	Priority date (*day/month/year*) 13 July 1999 (13.07.1999)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 39/395, 39/00; C07K 16/00, 01/00 and US Cl.: 424/134.1, 185.1, 192.1; 435/69.7; 530/387.3, 351

Applicant

BOLDER NIOTECHNOLOGY INC.

1. This written opinion is the first (first, etc,) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2 (a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension. See rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 13 November 2001 (13.11.2001) .

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Jessica H. Roark Telephone No. (703) 308-0196

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I. Basis of the opinion

1. With regard to the elements of the international application:*

☒ the international application as originally filed

☒ the description:
pages 1-62, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 63 and 64, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/fig NONE

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed."*

WRITTEN OPINION

International application No.
PCT/US. 336

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 6-14,22,23 and 26-37

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 6 are so unclear that no meaningful opinion could be formed *(specify)*:

Claim 6 is an improper multiple dependent claim as per PCT Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 7-14, 22-23 and 26-37.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 3-5 and 17-20 and 25	YES
	Claims 1-2, 15-16, 21 and 24	NO
Inventive Step (IS)	Claims 17-20 and 25	YES
	Claims 1-5, 15-16, 21 and 24	NO
Industrial Applicability (IA)	Claims 1-5, 15-21 and 24-25	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS
Please See Continuation Sheet

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

TIME LIMIT:
The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

V. 2. Citations and Explanations:

1. Claims 1-2 and 24 lack novelty under PCT Article 33(2) as being anticipated by US 5,650,150 (GILLIES).

US 5,650,150 teaches a fusion protein comprising a the cytokines IL-2, lymphotoxin, or GM-CSF joined either directly or via a linker sequence comprising a proteolytic cleavage site to an immunoglobulin domain (see entire document, especially claims 1, 3 and 7-11). In addition, a purified dimeric Ig fusion protein is taught, since the CH3-LT fusion protein forms dimers (e.g., column 8, especially lines 56-65), and can be purified (e.g., column 9, lines 25-43).

2. Claims 15-16 and 21 lack novelty under PCT Article 33(2) as being anticipated by US 5,073,627 (CURTIS et al.).

US 5,073,627 teaches a multimeric fusion protein comprising two or more members of the GH supergene family (GM-CSF and IL-3) joined with or without a peptide linker (see entire document, especially claim 1). In addition, a multimeric fusion protein wherein one of the members is GM-CSF is taught (e.g., claim 1).

3. Claim 2 and 24 lack novelty under PCT Article 33(2) as being anticipated by SHU et al.

SHU et al. teach a fusion protein comprising a first protein joined by a peptide linker to a fragment of an immunoglobulin domain, comprising the cytokine IL-2 linked via a GGGSGGG linker to the CH3 of an immunoglobulin heavy chain (see entire document, especially "Abstract". Purification of this dimeric Ig fusion protein is also taught (e.g. "Abstract" and Section 2.5).

4. Claims 15-16 and 21 lack novelty under PCT Article 33(2) as being anticipated by CURTIS et al.

CURTIS et al. teach a multimeric fusion protein comprising GM-CSF either linked directly or through a peptide linker to IL-3 (see entire document).

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

5. Claim 2 lacks novelty under PCT Article 33(2) as being anticipated by US 5,723,125 (CHANG et al.).

US 5,723,125 teaches a fusion protein comprising a human interferon linked to an immunoglobulin Fc via a peptide linker comprising Gly and Ser (see entire document, e.g., "Abstract"). US 5,723,125 also teaches that the incorporation of a linker sequence is useful to avoid formation of neoantigens in the fusion protein (e.g., column 3, especially lines 22-35).

6. Claims 1-5 and 24 lack an inventive step under PCT Article 33(3) as being obvious over EITHER US 5,650,150 (GILLIES), OR SHU et al., OR US 5,723,125 in view of ROBINSON et al.

The claims are drawn to various peptide linker sequences used to link a first protein to an immunoglobulin domain.

US 5,650,150 has been discussed supra and teach a first protein linked to an immunoglobulin domain, either directly or with a linker comprising a proteolytic cleavage site, and the dimeric protein's purification.

SHU et al. or US 5,723,125 likewise have been discussed supra and teach a first protein linked via a peptide linker sequence to an immunoglobulin domain.

Neither US 5,650,150, SHU et al. nor US 5,723,125 teach the exact linkers recited.

ROBINSON et al. teach various linkers, and that different linkers comprising various amount and sequence compositions of Gly and Ser can be used for any given fusion construct in order to optimize the stability of single chain proteins (see entire document).

Given the teachings of the references in view of ROBINSON et al., it would have been obvious to the ordinary artisan at the time the invention was made to select for and optimize various linker sequences depending upon the first protein linked to the immunoglobulin domain. The ordinary artisan would have been motivated to optimize this linkage in order to obtain a stable fusion protein. Given the teachings of the references, the ordinary artisan would have had a reasonable expectation of success in producing any particular linkers comprising varying ratios and sequences of Gly and Ser. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

7. Claims 1-5, 15-21 and 24-25 appear to have industrial applicability as defined by PCT Article 33(4) since the fusion proteins of the instant invention could be used in the various methods of stimulating cell growth.

---------- NEW CITATIONS ----------

US 5,073,627 A (CURTIS et al.) 17 December 1997. (17-12-1997), see entire document, especially "Abstract" and "Claims".

US 5,650,150 A (GILLIES) 22 July 1997 (22-7-1997), see entire document, especially "Claims".

ROBINSON et al. Optimizing the stability of single-chain proteins by linker length and composition mutagenesis. Proc. Natl. Acad. Sci. USA. May 1998, Vol. 95, pages 5929-5934; see entire document, especially "Discussion".